DRAFT STATEMENT
April 28, 2010
8:00 p.m.

NATIONAL INSTITUTES OF HEALTH
STATE-OF-THE-SCIENCE CONFERENCE STATEMENT
NIH State-of-the-Science Conference:
Preventing Alzheimer's Disease and Cognitive Decline
April 26–28, 2010

National Institutes of Health (NIH) consensus and state-of-the-science statements are prepared by independent panels of health professionals and public representatives on the basis of (1) the results of a systematic literature review prepared under contract with the Agency for Healthcare Research and Quality (AHRQ), (2) presentations by investigators working in areas relevant to the conference questions during a 2-day public session, (3) questions and statements from conference attendees during open discussion periods that are part of the public session, and (4) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the panel and is not a policy statement of NIH or the Federal Government.

The statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

Introduction

Alzheimer's disease is the most common cause of dementia. It was first described in 1906, when German psychiatrist and neuropathologist Alois Alzheimer observed the pathological hallmarks of the disease in the brain of a female patient who had experienced memory loss, language problems, and unpredictable behavior, and who at postmortem had abnormal clumps of protein (beta-amyloid plaques) and tangled bundles of protein fibers (neurofibrillary tangles) in the brain. An important breakthrough was the invention of a method for taking photographs through the lens of a microscope allowing the illustration of amyloid plaques and neurofibrillary tangles. Solomon Carter Fuller, an African American psychiatrist, invented this key innovation, the photomicrograph, in the early 1900s.

Since its first description, Alzheimer's disease diagnosis has undergone a transformation, from a rarely reported disorder to one of the most common disabling diseases among older individuals. The rapid aging of the U.S. population has reinforced the urgent need for prevention and treatment of all chronic diseases including Alzheimer's disease. In most individuals, cognitive health and performance remain stable over the lifetime, with only a gradual decline in short-term memory and processing speed. But for others, the decline in cognitive function progresses to a more serious state of cognitive impairment or into various forms of dementia. Mild cognitive impairment is a condition characterized by problems with memory, language, or other essential cognitive functions that are severe enough to be noticeable to others and are reflected on cognitive tests, but are not severe enough to interfere with daily life. Dementia is characterized by progressive global deterioration of cognitive abilities in multiple domains including memory

and at least one additional area—learning, orientation, language, comprehension, and judgment—severe enough to interfere with daily life.

Currently, Alzheimer's disease diagnoses account for 60 to 80 percent of all individuals with dementia, depending on the diagnostic and pathological criteria utilized. Up to 5.3 million Americans suffer from Alzheimer's disease, and these numbers are expected to grow with the aging of the baby boomer generation; the prevalence of mild cognitive impairment is thought to be even higher. Alzheimer's disease is the sixth leading cause of death in the United States and the fifth leading cause of death in Americans age 65 and older. Alzheimer's disease and other dementias cost more than $148 billion in the United States annually. Alzheimer's disease also exacts a significant toll from caregivers in terms of financial costs as well as on their own physical and mental well-being.

To date, numerous studies have attempted to describe the etiology and factors associated with the risk of development and progression of mild cognitive impairment and Alzheimer's disease; these studies have generated an abundance of theories on potential risk factors and therapies. Age is the strongest known risk factor for Alzheimer's disease, with most people diagnosed with the late-onset form of the disease after age 60. An early-onset familial form also occurs but is rare. Genetic, cardiovascular, and lifestyle factors also have been implicated.

The National Institute on Aging and the Office of Medical Applications of Research of the National Institutes of Health convened a State-of-the-Science Conference on April 26–28, 2010, to assess the available scientific evidence related to the following questions:

1. What factors are associated with the reduction of risk of Alzheimer's disease?

2. What factors are associated with the reduction of risk of cognitive decline in older adults?

3. What are the therapeutic and adverse effects of interventions to delay the onset of Alzheimer's disease? Are there differences in outcomes among identifiable subgroups?

4. What are the therapeutic and adverse effects of interventions to improve or maintain cognitive ability or function? Are there differences in outcomes among identifiable subgroups?

5. What are the relationships between the factors that affect Alzheimer's disease and the factors that affect cognitive decline?

6. If recommendations for interventions cannot be made currently, what studies need to be done to provide the quality and strength of evidence necessary to make such recommendations to individuals?

During the first 2 days of the conference, experts presented information on each of the key questions. After weighing the scientific evidence—including the data presented by the speakers and a formal evidence report from the Evidence-based Practice Center at Duke University's Clinical Research Institute commissioned by the Agency for Healthcare Research and Quality (available at http://www.ahrq.gov/clinic/tp/alzcogtp.htm)—an independent panel prepared and presented a draft of this state-of-the-science statement addressing the conference questions.

The panel review included relevant studies on the relationship of nutritional, medical factors (conditions and medications), and social/economic/behavioral, environmental, and genetic factors with mild cognitive impairment and/or Alzheimer's disease. The scope of the review was restricted to human studies conducted in developed countries—with sample sizes of at least 50 participants for randomized control trials and 300 for observational studies and a minimum duration between exposure to prevention interventions and outcomes—to assess success of interventions of 1 year for studies of mild cognitive impairment and 2 years for studies of Alzheimer's disease. The panel considered studies published in English with participants age 50 and older, of both sexes, and of all racial and ethnic populations. Studies were rated based on their quality, using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group criteria. The panel's charge was confined to answer questions related to prevention and not treatment of established Alzheimer's disease.

1. What factors are associated with the reduction of risk of Alzheimer's disease?

There is currently no evidence considered to be of even moderate scientific quality supporting the association of any modifiable factor (nutritional supplements, herbal preparations, dietary factors, prescription or nonprescription drugs, social or economic factors, medical condition, toxins, environmental exposures) with reduced risk of Alzheimer's disease.

What We Know

Genetic factors, particularly the apolipoprotein E (ApoE) gene variation, have strong evidence of association with the risk of Alzheimer's disease. Although it is hoped that improved understanding of genetic risk factors for Alzheimer's disease may ultimately lead to effective therapies for this disease, the observed genetic associations are currently clinically relevant largely as potential stratification factors in studies to identify additional risk factors and in clinical trials designed to test effectiveness of therapies.

A number of modifiable factors have been reported to show association with risk of Alzheimer's disease across multiple studies, but the overall scientific quality of the evidence is considered low. This indicates that additional studies on these factors are likely to alter, perhaps substantially, the magnitude or direction of the observed associations. These factors include other diseases, such as diabetes, elevated blood cholesterol in midlife, and depression, all reported to be associated with increased risk of Alzheimer's disease. Other factors reported to show association with Alzheimer's disease are relatively benign changes in diet, medication, or lifestyle that might allow individuals to feel more in control of their risk for Alzheimer's disease.

Among the factors that might be considered in this category are adequate levels of folic acid, adherence to a diet low in saturated fats and high in fruits and vegetables, use of statins, light to moderate use of alcohol, more years of education, higher levels of cognitive engagement, and participation in physical activities. All of these factors are reported to be associated with reduced risk of Alzheimer's disease. Current smoking, never having been married, and having low social support are all reported to be associated with increased risk of Alzheimer's disease. However, the evidence for association of all of these factors with Alzheimer's disease was considered to be of low quality. Consistent associations were not found for other vitamins, fatty acids, metabolic syndrome, blood pressure, plasma homocysteine, obesity and body mass index, antihypertensive medications, nonsteroidal anti-inflammatory drugs (NSAIDs), gonadal steroids, solvents, electromagnetic fields, lead, or aluminum.

Limitations

Among the challenges of interpreting the results of the studies on the diseases and other factors associated with Alzheimer's disease is the fact that the definition of Alzheimer's disease is not uniformly applied. Another key challenge in interpreting the studies is distinguishing the factors associated with Alzheimer's disease from those factors associated with other late-onset disorders that are commonly diagnosed in older individuals. For example, vascular disease also can lead to dementias, and because vascular disease is common in the elderly, it will often be present in individuals with Alzheimer's disease. Thus, it can be quite difficult to disentangle the factors associated with Alzheimer's disease because of their contribution to vascular disease and related dementias and those that are truly associated with Alzheimer's disease. Similarly, it is unclear whether some of the observed associations might simply reflect early features of Alzheimer's disease. The associations with depression, for example, might reflect an early stage of disease.

The primary limitation with most of these studies is the distinction between association and causality. Diseases are complex—determined and shaped by many variables. Factors that are reproducibly associated with disease, even when they are not contributing causally, can still be useful as potential predictors of risk. But the primary reason that association studies are conducted is to identify factors that might actually be contributing to risk of disease. A key problem with associations is that they often involve factors that are themselves correlated. For example, individuals with higher levels of education are also more likely to have higher levels of cognitive engagement. When a set of correlated factors shows an association with disease, it is difficult to determine whether any (or all) of the factors contributes causally to disease. Alternatively, one or more unobserved factors (correlated with the others) may actually account for the observed associations.

2. What factors are associated with the reduction of risk of cognitive decline in older adults?

Cognition is a combination of skills, including attention, learning, memory, language, visual spatial skills, and executive function, such as decisionmaking, goal setting, planning, and judgment. Decline in cognition ranges from the most severe forms of dementia, an example of which is Alzheimer's disease, to mild cognitive impairment and age-related cognitive decline.

Cognitive decline is multicausal, and mild cognitive impairment may not lead to dementias such as Alzheimer's disease. Neuropsychological testing for the above-mentioned skills over varying time periods has been the predominant method for the evaluation of cognitive change, but functional cognitive decline is only moderately associated with pathological changes typical of Alzheimer's disease. The idea of cognitive reserve (the mind's resilience to neuropathological damage of the brain) has developed to explain variances in ability to cope physiologically and mentally with existing pathology. Despite the hopeful insights provided by this concept, these issues have severely compromised the ability to design robust studies to determine factors that might prevent cognitive decline.

What We Know

For most factors, the available studies show either no association with cognitive decline or the evidence is inconclusive. Where an association was seen, the overall quality of the evidence was low. Many of the limitations stem from the fact that a good portion of the available evidence derives from studies that were originally designed and conducted to investigate conditions other than cognitive decline (e.g., cardiovascular disease, cancer). Cognitive decline is often a secondary or post-hoc interest and is evaluated with limited resources. The available information is compromised by important methodological limitations in the assessment of the outcome (cognitive decline) or exposures (factors) that characterize many of the studies conducted to date.

Limitations

Limitations in the evaluation of outcome include the lack of clear definition, criteria, and standardization for cognitive decline (cognitive decline is not a single entity and may have different etiologies). There are limitations in the evaluation of cognitive decline that characterize many of the studies conducted to date. Instruments used by different studies vary in their scope, and it is often difficult (or impossible) to compare results across studies and identify the reasons for inconsistency in findings. The ascertainment of cognitive decline is often limited to a single measurement at follow-up. This approach severely limits the ability to determine validly whether cognitive decline really exists, especially because cognitive decline is not linear and many factors affect cognitive performance and may change in the same individual from time to time. Many of the studies are limited by the relatively short follow-up time.

There are also limitations in the evaluation of exposures (factors). The studies to date differ widely in the quality of the measurements of important exposures (e.g., dietary factors, lifestyle habits, medications, health history, social factors, and engagement). Many of the available studies have characterized their participants at a single point in time.

The following discussion summarizes what we know about specific factors.

Nutritional and Dietary Factors. The available evidence does not support a clear role for most of the nutritional and dietary factors that have been examined. The most consistent evidence is available for the longer chain omega-3 fatty acids (often measured as fish consumption) that have been shown to be associated with a reduced risk of cognitive decline in several longitudinal

studies. For the other factors, the evidence varies from those studies with no consistent association (i.e., vitamin B, vitamin E, vitamin C, folate, beta-carotene) to those with very limited evidence suggesting a possible protective effect (a diet low in saturated fat and high in vegetable intake).

Medical Factors. Among the medical factors considered, a number of cardiovascular risk factors have been consistently associated with an increased risk of cognitive decline. Among these, high blood pressure has been more consistently associated, especially when relatively severe cognitive decline was examined. Diabetes also has been associated with an increased risk of cognitive decline, but this association is less consistent and appears to be more modest. Metabolic syndrome, a cluster of metabolic abnormalities associated with the incidence of cardiovascular disease, has been consistently associated with a modest risk of cognitive decline. For other medical factors, there is a lack of good-quality studies (e.g., sleep apnea, traumatic brain injury) or the findings are inconclusive (e.g., obesity).

Psychological and Emotional Health. Depression and depressive symptoms have been consistently found to be associated with mild cognitive impairment and cognitive decline.

Medications. No consistent epidemiological evidence exists for an association with either statins, antihypertensive medications, or anti-inflammatories. There are insufficient data to comment on cholinesterase inhibitors or memantine. The study results are made more difficult to interpret because of variation in formulations, dosage, duration, route of administration (i.e., postmenopausal estrogens), and the drug treatment effect (e.g., antihypertensive medications).

Socioeconomic Factors. Childhood socioeconomic status or cognitive milieu does not appear to be a strong influence on cognitive decline later in life. The evidence is inconsistent regarding the putative association between years of education and cognitive decline.

Social and Cognitive Engagement. The findings are inconsistent regarding living alone or being without a partner for any reason. However, there appears to be a more robust association between the loss of a spouse and cognitive decline. There is limited but inconsistent evidence suggesting that increased involvement in cognitive activities in later life is associated with slower cognitive decline and lower risk of mild cognitive impairment.

Physical Activity and Other Leisure Activities. Preliminary evidence suggests a beneficial association of physical activity and a range of leisure activities (e.g., club membership, religious services, painting, gardening) with the preservation of cognitive function.

Tobacco and Alcohol Use. There is evidence for an association between current smoking and increased risk of cognitive decline. The evidence for past smoking is less consistent. Results are inconsistent regarding the association between cognitive decline and alcohol use.

Genetic Factors. The majority of studies suggest that ApoE gene variation is associated with an increased rate of cognitive decline in elderly individuals, especially on some memory tasks and tasks of perceptual speed. The ApoE gene variation does not appear to affect all cognitive domains, and there is variability between studies.

3. What are the therapeutic and adverse effects of interventions to delay the onset of Alzheimer's disease? Are there differences in outcomes among identifiable subgroups?

Although numerous interventions have been suggested to delay Alzheimer's disease, the evidence is inadequate to conclude that any are effective. This conclusion is based on a review of published literature of randomized, controlled trials (RCTs), the most rigorous, highest quality evidence. RCTs are studies in which participants are allocated by chance alone to receive one or more treatment interventions. Because of the protracted course of Alzheimer's disease, our conclusions are based on RCTs that were at least 2 years in duration and adequately powered. Our conclusions do not reflect the existence of observational studies in which the investigator does not assign the exposure or treatment of interest to participants. However, information from these observational studies has formed, and will form, the basis for RCTs.

Assessment of Detailed Interventions

Vitamins, Nutrients, and Dietary Supplements. Results from a recent RCT of vitamin E found no evidence that this factor altered the onset of the Alzheimer's disease. Other nutritional factors (e.g., other vitamins, Mediterranean diet) may be beneficial, but there is not sufficient evidence to support this conclusion. It is possible that patients with vitamin deficiency may demonstrate a greater response than those without deficiency, but no trials have examined this issue. Gingko biloba was reported to have some benefit in small, short-term clinical trials. However, a recent, large long-term RCT comparing gingko biloba to placebo showed no reduction in the incidence of Alzheimer's disease, leading to the conclusion that there is not sufficient evidence to support the efficacy of gingko biloba.

Medications. Cholinesterase inhibitors are the most common treatment for mild to moderate Alzheimer's disease and have been the focus of several RCTs evaluating prevention of Alzheimer's disease. Although there is some disagreement in the literature, the entire body of evidence led us to conclude that this class of drugs is not effective in preventing Alzheimer's disease. RCTs of antihypertensive medications and hormone replacement (conjugated equine estrogen) also were negative with insufficient evidence for protection against Alzheimer's disease. Some available evidence shows that certain interventions have the opposite effect, increasing the incidence of Alzheimer's disease. Two RCTs of specific NSAIDs—rofecoxib, naproxen, and celecoxib—suggest an increased incidence of Alzheimer's disease with treatment. However, these studies have limitations due to the high dropout rate and early termination over concerns about toxicity. Two RCTs of conjugated equine estrogen, one combined with methyl progesterone, suggest an increased incidence of dementia (including Alzheimer's disease) with treatment. Together, these trials suggest that no known medication can be said to reliably delay the onset of Alzheimer's disease.

Other Factors. No RCTs were identified that evaluated the effects of cognitive engagement, physical activities, or other leisure activities for delaying the onset of Alzheimer's disease.

4. What are the therapeutic and adverse effects of interventions to improve or maintain cognitive ability or function? Are there different outcomes in identifiable subgroups?

Several interventions have been evaluated with respect to improving cognitive function or preventing cognitive decline. Despite some encouraging associations found in observational studies, RCTs of specific interventions have failed to *definitively* establish positive therapeutic effects on either maintaining or improving cognitive function or preventing cognitive decline. Although less attention has been given to identifying potential adverse effects, little evidence presented suggests that interventions designed to improve cognitive function either worsen it or produce unwanted side effects. There also are no data to draw any firm conclusions regarding differences in outcomes among identifiable subgroups. Some of the main reasons for the inability to identify successful interventions *may* include (1) lack of a validated and consistent definition of cognitive decline; (2) the small number of RCTs with cognitive decline as a primary outcome; (3) limitations of study design and analysis including short follow-up duration, biases and inconsistencies in study subject recruitment, small effect sizes, and confounding effects of multiple interrelated behaviors.

Assessment of Detailed Interventions

Vitamins, Nutrients, and Dietary Supplements. Results from several RCTs do not suggest any effect for vitamin supplementation in preventing cognitive decline. However, these trials used varying doses of the nutrients, failed to uniformly measure and monitor patients' cognitive function and baseline nutritional status, and had short and variable follow-up. Often, cognitive decline was measured as a secondary or tertiary outcome as part of other studies. For these reasons, these trials may have been underpowered.

In a single randomized trial complicated by poor compliance, gingko biloba co-administered with vitamin E failed to improve or maintain cognitive function in the elderly. In a single randomized trial of omega-3 fatty acids with only 26 weeks of follow-up, there appeared to be no effect on cognitive functioning. Another four trials in progress may revise this evidence, but at this time no interventional trials convincingly demonstrate that dietary supplements improve or maintain cognitive functioning.

Medications. With the exception of a single trial of antihypertensive medication in patients with hypertension, known vascular disease, and a history of stroke, the majority of the evidence suggests that antihypertensive treatment results in no cognitive benefit, whereas the value of these medications for hypertension is without question. Similarly, treatment with statins did not result in cognitive benefit. Low-dose aspirin and celecoxib also were found to be of no benefit, and naproxen was actually found to possibly increase cognitive decline. While there are several shortcomings of the trials examining the effect of gonadal steroids, including the type of steroid used, the duration and timing of use, the type of menopause (surgical or natural), and the mode

of delivery, randomized trials of estrogen have not been shown to prevent cognitive decline and the use of conjugated equine estrogen plus methyl progesterone may actually worsen cognitive outcome. Finally, multiple trials of cholinesterase inhibitors have shown no consistently positive effects on cognitive decline. Together, these data suggest that no currently available medications can prevent the onset of cognitive decline.

Cognitive Engagement. A single, large randomized trial of cognitive training (consisting of memory, reasoning, and speed) over a 5- to 6-week period with a subsequent booster period has shown modest benefits on cognitive functioning and a small but statistically significant effect on reducing the extent of age-related decline in cognitive function at a 5-year follow-up. This trial also showed a very small but statistically significant benefit on instrumental activities of daily living—for example, managing finances, managing medications, keeping house, and, in a subgroup analysis, benefit on driving performance in the elderly. However, these results from a single trial must be replicated to confirm the benefits of cognitive engagement on preventing cognitive decline over a longer time period and in study subjects with varying levels of baseline cognitive abilities before a firm recommendation can be made. It also will be important to assess the sustainability of these behaviors in a large, community-based sample of subjects where other less rigorous interventions showed no benefit.

Physical Activity. Some evidence from small interventional studies and selected observational studies suggests that increased physical activity, including walking, may help maintain or improve cognitive function in normal adults. A meta-analysis of several RCTs, many with methodological limitations, concluded there were insufficient data to state that aerobic activity improves or maintains cognitive function. However, a higher quality but small, randomized trial of physical activity in those with confirmed memory problems showed some modest benefit in reducing cognitive decline over an 18-month follow-up period. Although encouraging, these data should be viewed as preliminary. Work is ongoing to further investigate the benefits of physical activity.

5. What are the relationships between the factors that affect Alzheimer's disease and the factors that affect cognitive decline?

Imprecise and varied assessments of "age-associated cognitive decline," "mild cognitive impairment," and "Alzheimer's disease" in the existing literature prevent clear and concise answers to this question. These three terms refer to heterogeneous groups of conditions, and the existing literature leaves major gaps in knowledge, which must be addressed through research to provide adequate responses to this question.

What We Know

Factors associated with increased risk of Alzheimer's disease and cognitive decline are diabetes mellitus, ApoE gene variation, and current smoking and depression.

There is some limited evidence that estrogens and NSAIDs convey increased risk of Alzheimer's disease, but no evidence that these medications increase risk for age-associated cognitive decline. There is no consistent association of increased risk for Alzheimer's disease and age-associated cognitive decline conveyed by cholinesterase inhibitors, obesity, hypertension, and blood homocysteine levels.

Factors associated with decreased risk of Alzheimer's disease and cognitive decline were cognitive engagement (as indicated by literacy and social enrichment), physical activities in later life, and a diet low in saturated fat and high in vegetable intake. Light to moderate alcohol intake is reported to be associated with reduced risk of Alzheimer's disease, but results are inconsistent for cognitive decline.

There is no consistent association between Alzheimer's disease or cognitive decline and intake of gingko biloba, beta-carotene, flavonoids, multivitamins, and vitamins B12, C, and E.

Limitations

A consistent association does not imply that findings were robust: the data were often limited, and the quality of evidence was typically low. In addition, the risk modification effect of reported associations was typically small to moderate for Alzheimer's disease and small for cognitive decline.

6. If recommendations for interventions cannot be made currently, what studies need to be done to provide the quality and strength of evidence necessary to make such recommendations to individuals?

This review of the state of the science highlights the presence of critical gaps in current knowledge about the epidemiology of Alzheimer's disease and cognitive impairment. To date, numerous studies have attempted to describe the etiology and factors associated with risk of development and progression of cognitive decline and of Alzheimer's disease and have generated an abundance of theories on modifiable risk factors and therapies. However, these studies have failed to provide convincing evidence on the strength of these associations, and these results cannot be used as the basis to generate specific recommendations for preventive measures or interventions. This report underscores the need and rationale for conducting rigorous, state-of-the-art, methodologically sound research to address these deficiencies. The panel strongly recommends the following:

- Rigorous consensus-based diagnostic criteria for Alzheimer's disease should be improved and uniformly used across research studies. Research is critically required for identification of biomarkers associated with Alzheimer's disease and for further development of brain imaging techniques such as magnetic resonance imaging and positron emission tomography scanning to pinpoint pathological changes specific to Alzheimer's disease that could be assessed *in vivo* and serve as objective diagnostic

criteria. Alzheimer's disease is known to have a long latent period with hallmark pathological changes seen in the brain tissue of younger adults. Further research is required to understand and delineate the natural progression of Alzheimer's disease, to relate progression to pathological signs and clinical symptoms, and to determine (for example) whether depression and cognitive impairment are risk factors for the development of Alzheimer's disease or reflect early stages of the disease.

- An objective and consensus-based definition of mild cognitive impairment needs to be developed, including identification of the cognitive areas or domains of impairment, the recommended cognitive measures for assessment, and the degree of deviation from normal to meet diagnostic criteria. This consistency in definition and measurement is important to generate studies that can be pooled or compared to better assess risk factors and preventive strategies for cognitive decline and Alzheimer's disease.

- We encourage the use of a standardized, well-validated, and culturally sensitive battery of outcome measures (e.g., the NIH Toolbox) that can be used across research studies to assess relevant domains of cognitive functioning in a manner that is appropriate for the functional level of the population sample being studied (e.g., cognitively normal, mild cognitive impairment) and is responsive to detecting changes in cognitive function over time, and age-gender specific norms need to be established for comparison and objective assessment of disease severity. We recommend a comprehensive approach to outcomes assessment that accounts for the impact of cognitive decline on other domains of function and quality of life of both the affected person and his or her primary caregiver.

- The caregiver is a valuable source of information about the daily function of the elderly person with mild cognitive impairment or early Alzheimer's disease, and observational studies and RCTs should collect data from caregivers in a systematic manner.

- Following the model of other chronic disease epidemiology, large-scale, long-term population-based studies using precise, well-validated exposure and outcome measures are required to generate strong evidence on biological, behavioral/lifestyle, dietary, socioeconomic, and clinical factors that may have protective or adverse effects on risk of cognitive decline or Alzheimer's disease. Individuals in these studies should be followed from middle age into old age, with repeated measurements to take into account the duration and timing of exposures, as effects of various risk factors may be more acute and interventions more effective during critical windows of time throughout life. Furthermore, data from early life, either retrospective or prospective, are necessary to assess the importance of these influences on later cognitive outcomes.

- Existing cohorts from ongoing, large-scale, population-based studies—including longitudinal cohort studies of cardiovascular and noncardiovascular risk factors and outcomes, with rigorous, standardized measures of a wide range of exposures and longitudinal socioeconomic surveys that contain detailed health measures—should be explored for opportunities for timely, cost-effective analyses of the development of cognitive decline or Alzheimer's disease, provided that these outcomes are validly measured. Any associations found could be further tested by RCTs or new observational studies as appropriate.

- Studies should include women and men from socioeconomically and ethnically diverse populations to examine the incidence and prevalence of Alzheimer's disease and cognitive decline in these groups. Based on the successes to date of the existing collaborative efforts, it is clear that a collaborative research infrastructure (at both the national and international level) will be criticial in advancing our research goals.

- Research is necessary to identify specific population subgroups that may be at higher risk of developing cognitive impairment or Alzheimer's disease, based on nonmodifiable factors such as age, ethnicity, or gene variation (e.g., ApoE). Long-term studies on high-risk populations (particularly treatment-seeking individuals with symptoms of mild cognitive impairment) should be conducted to delineate risk factors for and natural progression to Alzheimer's disease and to identify the long-term outcomes and factors associated with improvement, decline, and stabilization of cognitive function.

- Building on the existing research infrastructure, additional research resources and platforms that facilitate longitudinal long-term assessments of the risk of cognitive decline and the risk of progression from cognitive decline to Alzheimer's disease need to be leveraged. For example, a large, multicenter Alzheimer's disease registry, following the models of cancer, would greatly expand opportunities for research and surveillance. In addition, observational studies within large healthcare delivery systems with defined populations and well-developed electronic health records could serve as a cost-effective research platform for studies of cognitive decline and Alzheimer's disease.

- A Web site should be established to continually update the American public in an ongoing way about which preventive interventions for Alzheimer's disease and cognitive decline have proven efficacy.

- Future research into the basic mechanisms of normal and pathological aging is critical to identify additional targets for prevention.

Conclusions

- Extensive research over the past 20 years has provided important insights on the nature of Alzheimer's disease and cognitive decline and the magnitude of the problem. Nevertheless, there remain important and formidable challenges in conducting research on these diseases, particularly in the area of prevention. There are numerous ongoing or planned investigations which may offer promising new insights regarding the causes and prevention of these diseases.

- Cognitive decline and Alzheimer's disease are major sources of morbidity and mortality worldwide. They pose a significant burden not only on affected individuals, but also on their caregivers and society in general.

- Firm conclusions cannot be drawn about the association of modifiable risk factors with cognitive decline or Alzheimer's disease.

- There is an absence of highly reliable consensus-based diagnostic criteria for cognitive decline, mild cognitive impairment, and Alzheimer's disease, and the available criteria have not been uniformly applied.

- There is insufficient evidence to support the use of pharmaceutical agents or dietary supplements to *prevent* cognitive decline or Alzheimer's disease. However, ongoing additional studies including (but not limited to) antihypertensive medications, omega-3 fatty acid, physical activity, and cognitive engagement may provide new insight into the prevention or delay of cognitive decline or Alzheimer's disease.

- Large-scale population-based studies and RCTs are critically needed to investigate *strategies to maintain cognitive function in individuals at risk for decline,* to identify *factors that may delay the onset of Alzheimer's disease* among individuals at risk, and to identify *factors that may slow the progression of Alzheimer's disease* among individuals already diagnosed with the disease.

State-of-the-Science Panel

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Planning Committee members provided their input at a meeting held August 19–21, 2008. The information provided here was accurate at the time of that meeting.

*****Dr. Nancy Andreasen stepped down as panel chair on January 20, 2010, due to a relationship that was unforeseen to be a possible conflict of interest; we thank her for her invaluable service in this process.

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